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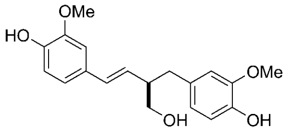
Zinc-Catalyzed Chemoselective Reduction of Esters to Alcohols

Shoubhik Das, Konstanze Möller, Kathrin Junge, and Matthias Beller*[a]

Functionalized alcohols are of importance for the manufacture of pharmaceuticals, agrochemicals, dyes, and numerous bioactive compounds (see below for selected examples of bioactive alcohols). Regarding their synthesis, the reduction of esters to the corresponding alcohols provides a straightforward access.[1] Notably, for special products and on a laboratory scale, traditional boron and aluminium hydride-mediated reductions still prevail.[2] Compared to these stoichiometric reactions, catalytic methods offer more versatile strategies and might allow for improved selectivity.[3]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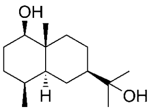
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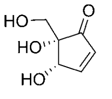
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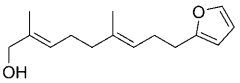
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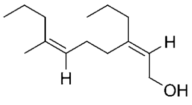
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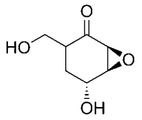
epi-epoxydon

Evidently, catalytic hydrogenation represents an ideal method for the reduction of esters, but sometimes low functional group tolerance and the necessity to use high pressure autoclaves impair its general use.[4] Although heterogeneous hydrogenation of fatty esters is performed in industry on bulk scale,[5] it needs high temperatures (200–300 °C) along with high hydrogen pressures (200–300 atm). On the other hand, homogeneously catalyzed hydrogenations have been only scarcely investigated until recently.[6]

Relative to hydrogenations, catalytic hydrosilylations are a well-accepted tool, which are operationally simple to perform and often allow for improved chemoselectivity and regioselectivity under mild conditions.[7] Hence, during the last decade metal-catalyzed hydrosilylations of esters have received considerable interest. To date, various catalyst systems including Rh,[8] Ru,[9] Mo,[10] Ti,[11] In,[12] Mn,[13] Pd,[14] organo zinc,[15] and boron compounds[16] have proven to be effective for this reduction. Nevertheless, the development of a cost-effective, efficient, and highly selective catalyst for this transformation is still desirable because most of the known protocols either require expensive silanes or have limited functional group tolerance.

The abundant availability, low toxicity and biomimetic nature[17] of zinc makes it a highly attractive candidate for catalysis. Based on our recent study on the zinc-catalyzed reduction of amides,[18] herein we report a general and improved catalytic hydrosilylation of esters to generate alcohols. Notably, excellent chemoselectivity is achieved in the presence of other reducible functional groups.

Initially, the reaction of methyl phenylacetate **1a** with $(EtO)_2MeSiH$ in THF was investigated as a model system to identify and optimize the critical reaction parameters (Table 1). As expected, no reaction occurred in the absence of any catalyst (Table 1, entry 1). In contrast, 10 mol % of inexpensive $Zn(OAc)_2$ was an excellent catalyst and gave 2-phenylethanol **1b** in 90 % yield, after hydrolysis with 25 % KOH in methanol (Table 1, entry 2). However, after applying lower catalyst loadings of 7.5 and 5 mol % the yield decreased to 70 and 45 %, respectively (Table 1, entries 3 and 4). Surprisingly, other zinc sources such as ZnF_2, $ZnBr_2$, ZnI_2, $Zn(ClO_4)_2\cdot 6H_2O$, and $Zn(NO_3)_2\cdot 6H_2O$ were inactive and only $Zn(2\text{-ethyl hexanoate})_2$ and $ZnCl_2$ showed a little activity (Table 1, entries 13–19). Other metal acetates (such as Cu and Fe) were also inactive (Table 1, entries 11–12). To exclude the influence of potential precious metal contaminants in the catalyst precursor we also used zinc acetate from different suppliers (ABCR, Sigma Aldrich, and Acros). In all cases similar yields of the product were obtained in the model reaction.

Next, we started to investigate the influence of different silanes on the reaction. In addition to $(EtO)_2MeSiH$, several silanes such as $PhSiH_3$, $PhSiH_2$, and $(EtO)_3SiH$ were also active (Table 1, entries 5–7). However, disilanes like tetramethyldisiloxane (TMDS) or polysilanes like polymethylhydrosiloxane (PMHS) were completely inactive under our reaction conditions and only the starting ester was recovered after the reaction. It should be noted that the observed differences in reactivity of silanes combined with the possibility to use different catalysts allows for a tuning of chemoselectivity of multiple substituted substrates. This is not possible with classic organometallic hydrides or in reactions with hydrogen. Scale up of the model reaction to 20 mmol resulted in no problems and produced phenylethanol (**1b**) in 90 % yield after concomitant hydrolysis.

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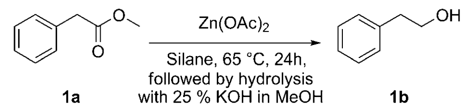
[a] S. Das, K. Möller, Dr. K. Junge, Prof. Dr. M. Beller
Leibniz-Institut für Katalyse e.V. an der Universität Rostock
Albert-Einstein-Str. 29a
18059 Rostock (Germany)
Fax: (+49) 381-1281-51113
E-mail: matthias.beller@catalysis.de

Table 1. Zinc-catalyzed reduction of methyl phenylacetate.[a]



Entry	Catalyst	[mol %]	Silane	[equiv]	Solvent	Yield[b] [%]
1	–	–	(EtO)$_2$MeSiH	3	THF	–
2	Zn(OAc)$_2$	10	(EtO)$_2$MeSiH	3	THF	90
3	Zn(OAc)$_2$	7.5	(EtO)$_2$MeSiH	3	THF	70
4	Zn(OAc)$_2$	5	(EtO)$_2$MeSiH	3	THF	45
5	Zn(OAc)$_2$	10	Ph$_2$SiH$_2$	3	THF	81
6	Zn(OAc)$_2$	10	(EtO)$_3$SiH	3	THF	90
7	Zn(OAc)$_2$	10	PhSiH$_3$	2	THF	82
8	Zn(OAc)$_2$	10	PMHS	5	THF	–
9	Zn(OAc)$_2$	10	Et$_3$SiH	3	THF	16
10	Zn(OAc)$_2$	10	TMDS	3	THF	–
11	Cu(OAc)$_2$	10	(EtO)$_2$MeSiH	3	THF	–
12	Fe(OAc)$_2$	10	(EtO)$_2$MeSiH	3	THF	–
13	ZnF$_2$	10	(EtO)$_2$MeSiH	3	THF	–
14	ZnCl$_2$	10	(EtO)$_2$MeSiH	3	THF	13
15	ZnBr$_2$	10	(EtO)$_2$MeSiH	3	THF	–
16	ZnI$_2$	10	(EtO)$_2$MeSiH	3	THF	–
17	Zn(ClO$_4$)$_2$·6H$_2$O	10	(EtO)$_2$MeSiH	3	THF	–
18	Zn(NO$_3$)$_2$·6H$_2$O	10	(EtO)$_2$MeSiH	3	THF	–
19	Zn(C$_5$H$_{11}$COOEt)$_2$	10	(EtO)$_2$MeSiH	3	THF	15
20	Zn(OAc)$_2$	10	(EtO)$_2$MeSiH	3	Toluene	90

[a] Reaction conditions: **1a** (1.0 mmol), catalyst (10 mol %), silane, and solvent ($T = 65$ °C, 3 mL) for 24 h. [b] Determined by GC with hexadecane as an internal standard.

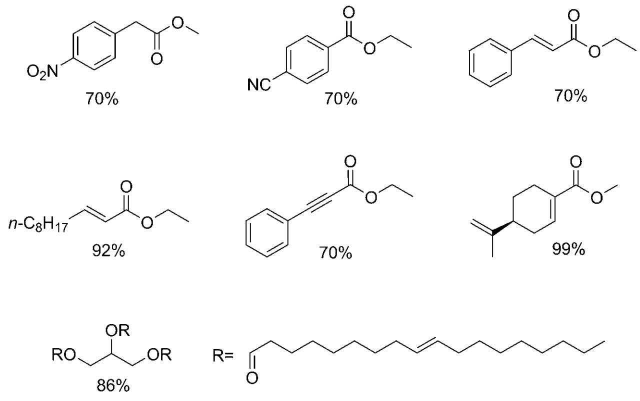
Once the optimized reaction conditions were identified, the scope and limitations of the zinc-catalyzed reduction of esters using (EtO)$_2$MeSiH were explored. A variety of esters, including aromatic, aliphatic, heteroaromatic, and heterocyclic esters were reduced smoothly to the corresponding alcohols (Table 2). Notably, aromatic esters were completely unreactive at 65 °C, but increasing the reaction temperature to 100 °C produced the corresponding alcohols in excellent yields (Table 2, entries 7–8). Substitution with bulkier groups on both the carbonyl and the alcohol side of the ester did not decrease the product yield (Table 2, entries 2–4 and 9). In fact, the yield increased for the substitution of methyl, ethyl or *n*-butyl groups by an isopropyl group on the alcohol part of the ester. In addition, electron-withdrawing and electron-donating substituents on the aryl part behaved similarly. Heteroarenes, as well as heterocyclic and alicyclic compounds, do not interfere with the ester reduction, giving the corresponding alcohols in good to very good yields (Table 2, entries 10–13).

The synthesis of optically pure 1,2-diols, an important class of chiral intermediates, is demonstrated by the reduction of methyl mandelate towards 1-phenyl-1,2-ethanediol (Table 2, entry 9). No racemization or loss of the original enantioselectivity was observed. However, efforts to reduce chiral amino acid esters gave a mixture of products.

After demonstrating the general applicability, we were interested in the functional group tolerance of our catalytic system. Hence, we studied the reactivity of more challenging substrates that might undergo additional reductive transformations. Such chemoselective reductions of esters are particularly interesting for the organic synthesis of multifunctional molecules.

As shown in Scheme 1, esters were reduced in the presence of nitro and nitrile groups, as well as triple bonds, isolated and conjugated double bonds. To our delight, none of these functional groups were reduced. In addition, methyl perilate also underwent selective ester reduction in the presence of an isolated and conjugated double bond to give perillyl alcohol in excellent yield. It should be noted that the traditional synthesis of perillyl alcohol involves additional protection and deprotection steps.

In summary, we have established a general zinc-catalyzed reduction of esters with inexpensive (EtO)$_2$MeSiH. In particular, the operational simplicity and the high functional group tolerance make this procedure attractive for organic synthesis without the need for protecting and deprotecting steps.



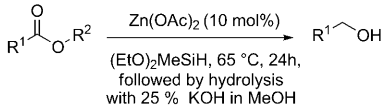
Scheme 1. Functional group tolerance: Reaction conditions; ester (1 mmol), Zn(OAc)$_2$ (10 mol %), and (EtO)$_2$MeSiH (3 mmol) in THF (3 mL). Yields were determined by GC analysis.

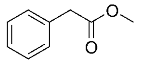
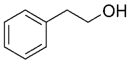
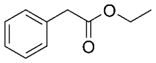
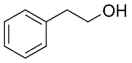
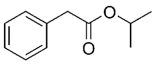
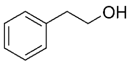
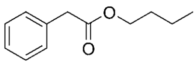
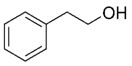
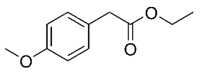
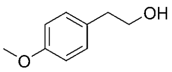
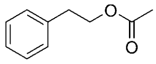
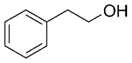
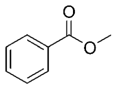
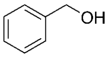
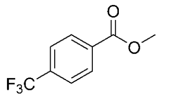
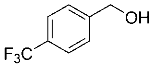
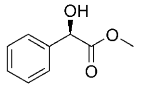
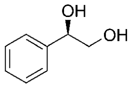
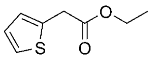
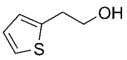
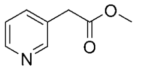
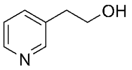
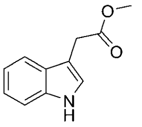
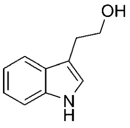
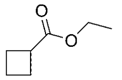
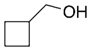
Experimental Section

General remarks: All reagents were used as purchased from commercial suppliers (Aldrich, Fluka, Merck, etc.) without further purification. GC analyses were performed with a Hewlett Packard HP 6890 model spectrometer. GC calibrations for ester and alcohols were carried out with authentic samples and hexadecane as an internal standard.

General procedure for ester reduction: A 10 mL oven dried Schlenk tube containing a stirring bar was charged with zinc acetate (0.1 mmol). Dry

Table 2. Zinc-catalyzed reduction of esters to alcohols.[a]



Entry	Esters (**a**)	Alcohols (**b**)	Yield[b] [%]
1			90 82[c]
2			82
3			98
4			76
5			81
6			83
7[d]			83
8[d]			91
9			76
10			81
11			70[c]
12			72
13[d]			65[e]

[a] Reaction conditions: Ester (1 mmol), Zn(OAc)$_2$ (10 mol%), (EtO)$_2$MeSiH (3 mmol), and THF (3 mL). [b] Yield was determined by GC analysis [c] Yields of isolated product. [d] Solvent: toluene, $T=100$ °C. [e] Product is water soluble.

THF (2 mL) or toluene (2 mL) and methyldiethoxysilane (3 mmol) were added respectively after purging the Schlenk tube with argon. The resulting mixture was stirred for 30 min at 65 °C. Then, the respective ester (1 mmol) in dry THF (1 mL) or toluene (1 mL) was transferred to the reaction solution under argon. The mixture was stirred at 65 °C or 100 °C for 24 h and monitored by TLC. After complete disappearance of the substrate, the reaction mixture was vigorously stirred with the internal standard (hexadecane, 100 μL) and 25% KOH in MeOH solution (5 mL) in a 25 mL conical flask overnight and then extracted with ethyl acetate (3×5 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude material was then dissolved in ethyl acetate and a sample was taken, which was subjected to GC analysis. For water soluble products (Table 2, entry 13), the yields were determined by GC analysis without further manipulations.

Purification of isolated compounds: In general, products were purified by using silica gel chromatography to afford the pure desired product. 2-Phenylethanol (**1b**): ethyl acetate/hexane, (70:30, R_f: 0.62), yield: 82%. 2-(3-Pyridyl)ethanol (Table 2, entry 11b) : ethyl acetate/hexane (90:10, R_f: 0.40), yield: 70%.

Acknowledgements

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Keywords: alcohols · catalysis · chemoselectivity · reduction · zinc

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